54. A protein comprising an HIV Tat protein or an immunogenic derivative thereof linked to an HIV Nef protein or an immunogenic derivative thereof in Nef-Tat or Tat-Nef orientation.

REMARKS

Claims 32-54 remain in this application. Claims 32-54 have been rejected. Claims 32-38 and 54 have been amended. Claims 32-38 and 54 have been amended for the following reasons:

Claim 32 - to define the composition as an immunogenic composition and to define the protein derivative as capable of inducing an immunoprotective response;

Claims 33-38 - to define the protein derivatives, including mutants, as capable of inducing an immunoprotective response; and

Claim 54 - to define the protein derivative as capable of inducing an immunoprotective response.

Attached hereto is a marked up version of the changes made to the specification and claims by the current amendment. The attached page is captioned **"Version with markings to show changes made."**

Objections to the Specification

Applicants have amended the specification to include a reference to related applications.

Drawings

Applicants are submitting final, corrected drawings herewith.

Claim Objection

Claim 32 has been amended to delete the reference to the Tat fusion partner and the Nef fusion partner.

Rejection Under 35 USC §112, First Paragraph - Claims 32-53

The Examiner rejected claims 32-53 for not being enabled because of the term "vaccine." While Applicants disagree with the Examiner's definition of the term vaccine and

the Examiner's position that the specification is not enabling for claims directed to a vaccine, Applicants have amended claim 32 to change "vaccine composition" to "immunogenic composition."

Withdrawal of the rejection of the claims under 35 U.S.C. §112, first paragraph, is respectfully requested.

Rejection Under 35 USC §112, First Paragraph - Claims 32, 35, 36 and 50-54

The Examiner rejected claims 32, 36 and 50-54 for not being enabled because the specification does not provide enough information regarding mutations in the proteins. Applicants disagree. The specification, p. 3, lines 6-12, teaches that deletions, additions or substitutions within Tat and Nef are included in the present invention and examples of mutants are given. Further, the specification on p.18, lines 4-6 teaches that mutant Tat proteins must be biologically inactive while maintaining immunogenic epitopes. Given this information, one skilled in the art would have known at the time of filing the nature of the mutations that could be tried, and the biological end result that is desirable. The same criteria also apply to the Nef-Tat fusion protein containing any such mutations. In any event, Applicants amended the claims to define the mutants as being immunogenic.

Withdrawal of the rejection of the claims under 35 U.S.C. §112, first paragraph, is respectfully requested.

Rejection Under 35 USC §112, First Paragraph - Claims 32, 35 and 50-54

The Examiner rejected claims 32, 35 and 50-54 for not being enabled because the specification does not provide enough information regarding the alternate orientations of the chimeric fusion protein. Applicants respectfully submit that the orientation of Nef, Tat and fusion partner is not critical to the invention. A fusion partner may be linked to either protein in either orientation.

Withdrawal of the rejection of the claims under 35 U.S.C. §112, first paragraph, is respectfully requested.

Applicants respectfully requests that a timely Notice of Allowance be issued in this case.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the specification:

Page 1 has been amended as follows:

FUSION PROTEINS COMPRISING HIV-1 TAT AND/OR NEF PROTEINS

This application is a 371 of PCT/EP98/06040, filed September 17, 1998, which claims priority from GB application 9720585.0, filed on September 26, 1997

The present invention relates to novel HIV protein constructs, to their use in medicine, to pharmaceutical compositions containing them and to methods of their manufacture.

In particular, the invention relates to fusion proteins comprising HIV-1 Tat and/or Nef proteins.

HIV-1 is the primary cause of the acquired immune deficiency syndrome (AIDS) which is regarded as one of the world's major health problems. Although extensive research throughout the world, has been conducted to produce a vaccine, such efforts thus far, have not been successful.

Non-envelope proteins of HIV-1 have been described and include for example internal structural proteins such as the products of the *gag* and *pol* genes and, other non-structural proteins such as Rev, Nef, Vif and Tat (Greene et al., New England J. Med, **324**, 5, 308 et seq (1991) and Bryant et al. (Ed. Pizzo), Pediatr. Infect. Dis. J., **11**, 5, 390 et seq (1992).

HIV Nef and Tat proteins are early proteins, that is, they are expressed early in infection and in the absence of structural proteins.

According to the present invention there is provided a protein comprising

(d) an HIV Nef protein or derivative thereof linked to either (i) a fusion partner or (ii) an HIV Tat protein or derivative thereof; or

(e) an HIV Tat protein or derivative thereof linked to either (i) a fusion partner or (ii) an HIV Nef protein or derivative thereof; or

(f) an HIV Nef protein or derivative thereof linked to an HIV Tat protein or derivative thereof and a fusion partner.

By 'fusion partner' is meant any protein sequence that is not Tat or Nef.

Preferably the fusion partner is protein D or its' lipidated derivative Lipoprotein D, from Haemophilius influenzae B. In particular, it is preferred that the N-terminal

In the claims:

Claims 32-38 and 54 have been amended as follows:

32. (Amended) [A vaccine] An immunogenic composition which comprises a protein comprising

(a) an HIV Tat protein or an immunogenic derivative linked to [either (i) a fusion partner or (ii)] an HIV Nef protein or an immunogenic derivative thereof; or

(b) an HIV Nef protein or an immunogenic derivative linked to [either (i) a fusion partner or (ii)] an HIV Tat protein or an immunogenic derivative thereof; or

(c) an HIV Nef protein or an immunogenic derivative linked to an HIV Tat protein or an immunogenic derivative thereof and a fusion partner,

in admixture with a pharmaceutically acceptable excipient.

33. (Amended) A composition as claimed in claim 32, comprising a Tat-Nef fusion protein or an immunogenic derivative thereof.

34. (Amended) A composition as claimed in claim 32, comprising a Nef-Tat fusion protein or an immunogenic derivative thereof.

35. (Amended) A composition according to claim 32, wherein the derivative of the Tat protein is [a] an immunogenic mutated Tat protein.

36. (Amended) A composition according to claim 32, wherein the derivative of the Nef protein is [a] an immunogenic mutated Nef protein.

37. (Amended) A composition as claimed in claim 32, wherein the fusion partner is a lipoprotein or an immunogenic derivative thereof.

38. (Amended) A composition as claimed in claim 37, wherein the lipoprotein is Haemophilus Influenza B protein D or an immunogenic derivative thereof.

54. (Amended) A protein comprising an HIV Tat protein or an immunogenic derivative thereof linked to an HIV Nef protein or an immunogenic derivative thereof in Nef-Tat or Tat-Nef orientation.